Kinetics of tumor size and peritumoral brain edema before, during, and after systemic therapy in recurrent WHO grade II or III meningioma

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Abstract: BACKGROUND The efficacy of systemic antineoplastic therapy on recurrent World Health Organization (WHO) grades II and III meningiomas is unclear. METHODS We performed a retrospective multicenter analysis of serial cranial MRI in patients with recurrent WHO II and III meningiomas treated with antineoplastic systemic therapies. Growth rates for tumor volume and diameter, as well as change rates for edema size, were calculated for all lesions. RESULTS We identified a total of 34 patients (23 atypical, 11 anaplastic meningiomas) with a total of 57 meningioma lesions who had been treated at 6 European institutions. Systemic therapies included bevacizumab, cytotoxic chemotherapy, somatostatin analogues, and tyrosine kinase inhibitors. Overall, tumor growth rates decreased during systemic therapy by 51% for tumor diameter and 14% for tumor volume growth rates compared with the period before initiation of systemic therapy. The most pronounced decrease in meningioma growth rates during systemic therapy was evident in patients treated with bevacizumab, with a reduction of 80% in diameter and 59% in volume growth. Furthermore, a decrease in size of peritumoral edema after initiation of systemic therapy was exclusively observed in patients treated with bevacizumab (-107%). CONCLUSIONS Our data indicate that systemic therapy may inhibit growth of recurrent WHO grades II and III meningiomas to some extent. In our small cohort, bevacizumab had the most pronounced inhibitory effect on tumor growth, as well as some anti-edematous activity. Prospective studies are needed to better define the role of medical therapies in this tumor type.

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Kinetics of tumor size and peritumoral brain edema before, during and after systemic therapy in recurrent WHO grade II or III meningioma

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Abstract

Background: The efficacy of systemic antineoplastic therapy on recurrent WHO II and III meningiomas is unclear.

Methods: We performed a retrospective multicenter analysis of serial cranial magnetic resonance images (MRI) in patients with recurrent WHO II and III meningiomas treated with antineoplastic systemic therapies. Growth rates for tumor volume and diameter, as well as change rates for edema size were calculated for all lesions.

Results: We identified a total of 34 patients (23 atypical, 11 anaplastic meningiomas) with a total of 57 meningioma lesions that had been treated at six European institutions. Systemic therapies included bevacizumab, cytotoxic chemotherapy, somatostatin analogues, tyrosine kinase inhibitors. Overall, tumor growth rates decreased during systemic therapy by 51% for tumor diameter and 14% for tumor volume growth rates compared to the period before initiation of systemic therapy. The most pronounced decrease in meningioma growth rates during systemic therapy was evident in patients treated with bevacizumab with a reduction of 80% in diameter and 59% in volume growth. Furthermore, a decrease in size of peritumoral edema after initiation of systemic therapy was exclusively observed in patients treated with bevacizumab (-107%).

Conclusions: Our data indicate that systemic therapy may inhibit growth of recurrent WHO II and III meningiomas to some extent. In our small cohort bevacizumab had the most pronounced inhibitory effect on tumor growth and in addition some anti-edematous activity. Prospective studies are needed to better define the role of medical therapies in this tumor type.

Key words: Atypical meningioma, anaplastic meningioma, chemotherapy, bevacizumab, anti-angiogenesis

INTRODUCTION

Meningiomas are the most frequent primary intracranial tumors in adults according to local and international brain tumor registries with an incidence rate of about 30% with a female predominance, followed by glioblastoma and pituitary adenoma.[1,2] Based on the WHO classification, meningiomas are histopathologically classified and graded into three different subgroups: benign meningiomas (WHO I), atypical meningiomas (WHO II) and anaplastic or malignant meningiomas (WHO III).[3] The majority of these subgroups are benign meningiomas, followed by atypical (up to 20% of all meningiomas) and anaplastic (about 1-3% of all meningiomas) meningiomas.[1]

While benign meningiomas are usually curable by surgery, atypical and anaplastic meningiomas are characterized by aggressive behavior and a high recurrence rate.[3] No accepted therapy standard exists for meningiomas after exhaustion of surgical and radiotherapeutic options. A variety systemic antineoplastic therapy including hydroxyurea, temozolomide, irinotecan, interferon-alpha, mifepristone, octreotide analogues, megestrol acetate, bevacizumab, imatinib, erlotinib, and gefitinib have been investigated in small studies and are being used in the clinical setting.[4-13] However, the validity of the available studies is limited by small sample sizes, retrospective study designs, heterogeneous patient populations, lack of control arms and varying response criteria, thus rendering the benefit of these drugs unclear.[14]

In the present study, we aimed to analyze the growth rates of recurrent WHO II and III meningiomas before, during and after treatment with systemic agents in order to provide novel information on the effect of drug treatment on the disease course.

MATERIAL AND METHODS

Patients

Institutional review board approval for this retrospective European multicenter study was obtained from each participating institution. All participating institutions were asked to provide radiological as well as predefined epidemiological and clinical data of the patients using a prepared form (see **Supplement 1**).

The inclusion criteria were as follows: (1) patient has histological diagnosis of WHO grade II or grade III meningioma according to 2007 WHO criteria; (2) patient has received systemic antineoplastic therapy for tumor recurrence after previous operation and/or radiotherapy; (3) availability of digital data sets of multiple MR examinations taken before, during and after the administration of systemic antineoplastic therapy.

Patient recruitment per institution was as follows: institution 1 (Vienna, n = 14), institution 2 (Leuven, n = 5), institution 3 (Lille, n=4), institution 4 (Zurich, n=4), institution 5 (Aarau, n=4) and institution 6 (Essen, n=3). First radiological diagnosis of meningioma was made between December 2002 and December 2013 and systemic antineoplastic therapy commenced between October 2005 and October 2013.

Image acquisition

All patients received an MRI examination with a routine clinical imaging protocol of the brain. In total 224 MRI examinations were included. The mean duration between two MRI examinations was 116 days (standard deviation (SD) 88 days). Each MRI examination included at least one T1-weighted sequence without and with contrast enhancement. In

addition, a T2-weighted sequence was performed in 90.6% of all MRI examinations (203 out of 224 MRI examinations).

Image analysis

The anonymized radiological data for participating patients from all institutions were collected in form of digital data. The MR images were qualitatively evaluated at institution 1 on a PACS (Picture Archiving and Communication System, Centricity, GE Healthcare) workstation by an experienced neuroradiologist (J.F.) regarding their usability for further postprocessing. Image postprocessing was performed using an open-source software (MRIcron).[15] Maximum tumor diameter, tumor volume and the volume of peritumoral edema were measured for each of the 224 MRI examinations by the same neuroradiologist (J.F.), blinded to all clinical patient data. T1-weighted post-contrast images were selected to determine the maximum tumor diameter as well as the tumor volume. The T2-weighted images were used to depict tumor edema. Maximum tumor diameter was defined as the biggest diameter of the contrast-enhanced tumor area measured in axial, coronal or sagittal image dimension. Tumor volume was automatically calculated on the basis of multiple manually defined regions of interests (ROI) including the whole contrast enhancing tumor area as well as cystic parts of the tumor in the T1-weighted post contrast sequences. Analogous to the tumor volume, peritumoral edema was determined using multiple ROI including the peritumoral hyperintense signal alterations in T2-weighted images, excluding contrast-enhancing tumor areas.

Statistical analysis

Resulting measurements from tumor volume, maximum tumor diameter, and the volume of peritumoral edema were submitted for further analysis. All lesions were subdivided into 3 different subgroups related to patient`s therapy status. The subgroup “pre-therapeutic”

represents all meningiomas before systemic therapy, the subgroup “therapeutic” included a pre-therapeutic baseline measurement within 4 weeks before the start of systemic therapy, all measurements during systemic therapy and the first measurement after systemic therapy if it was performed within 4 weeks after the completion of systemic therapy. All measurements after the systemic therapy are summarized in the “post-therapeutic” subgroup.

Measurements of maximum tumor diameter, maximum tumor volume and maximum peritumoral edema volume of every lesion were used to derive gradients of decrease and increase, which were specified as average growth rates for tumor volume and diameter and average change rates for edemas throughout the manuscript. Growth and change rates were defined as the decrease or increase in tumor diameter, tumor volume or peritumoral edema volume over a period of time (t), expressed as cm/t and cm^3/t, respectively. The time period was determined by the average MR follow-up interval of the lesions. Pearson correlation coefficient was used to assess the relation between the calculated growth rates of tumor diameter and tumor volume.

A positive growth rate indicated an increase of tumor diameter, tumor volume or edema volume, while a negative growth rate reflected a decrease of the different measurements. A growth rate of zero indicated no change in volume or diameter, respectively.

Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, MI, USA), version 20.0 was used for descriptive statistics of the cohorts. Visualizations were performed in MATLAB (Matlab 7.14.0, Release 2012a, Mathworks Inc., Sherborn, MA, USA). Testing for group differences between therapies was not utilized because of the small and unbalanced sample size.

RESULTS

Patient characteristics

We identified 34 patients with a total of 57 meningioma lesions that had been treated in six European institutions. Twenty-three patients (68%) had atypical meningiomas and 11 patients (32%) had anaplastic meningiomas. Systemic therapies included bevacizumab (n=5), cytotoxic chemotherapy (n= 9), somatostatin analogues (n=9), tyrosine kinase inhibitors (n=7). In 4 patients radiological data during systemic therapy were not available, therefore these patients were only included in the "pre-therapeutic" subgroup. Detailed patient´s baseline characteristics and the types of administered systemic therapies are given in **Supplement 2** and **Supplement 3.**

Thirty-two meningiomas were analyzable in the "pre-therapeutic" time window, 37 meningiomas in the "therapeutic" time window, and 26 in the "post-therapeutic" time window. The mean time period was 140 days (SD = 124 days, range = 13 – 637 days; mean number of MR examinations = 3.65, range = 2 - 6) for all pre-therapeutic MR examinations, 78 days (SD = 23 days, range = 41 - 156 days; mean number of MR examination = 3.13, range = 2 - 7) during systemic therapy and 142 days (SD = 79 days, range = 21 – 334 days; mean number of MR examination = 3.92, range = 2 - 7) for all post-therapeutic MR examinations.

Analysis of solid tumor lesions

Measurements of maximum tumor diameter and tumor volume were represented as average

growth rates, and further subdivided in “pre-therapeutic” lesion (n=32), “therapeutic” lesion (n=37) and “post-therapeutic” lesion (n=26) values. Overall, diameter and volume growth rate values of the tumor lesions showed a high correlation in total (Pearson correlation coefficient r=0.722; p= 1.4903*10^-16), in the pre-therapeutic (r= 0.794; p=5.8995*10^-8), therapeutic (r=0.52; p= 0.001), and post-therapeutic (r=0.892; p=9.144*10^-10) subgroups.

Table 1 and **Figures 1A, 1B and 2A, 2B** detail the tumor growth rates per time window and type of administered therapy. Overall, the mean tumor growth rates decreased by 51% for tumor diameter and 14% for tumor volume in the “therapeutic” period compared to the “pre-therapeutic” period. Comparing the growth rates between the different therapy types, we observed the highest decrease of growth rate from the “pre-therapeutic” to the “therapeutic” period in patients treated with bevacizumab (diameter: -80%, volume: -59%), followed by the subgroup of patients treated with chemotherapy (diameter: -54%, volume: +7%) and tyrosine kinase inhibitors (diameter: -40%, volume: -29%). Interestingly, in the post-therapeutic period patients treated with bevacizumab showed the highest increase with 200% in growth rates with regard to tumorous lesion diameter and the second highest increase in terms of tumor volume with 50% in comparison to the “therapeutic” period. The lowest growth rates in the post-therapeutic period were observed with tyrosine kinase inhibitors, both with regard to tumor diameter and tumor volume.

Furthermore, tumor growth rates were subdivided, regarding tumor histology, into tumor diameter and volume growth rates of WHO grade II meningiomas and WHO grade III meningiomas per time window in **Table 2**. In the “pre-therapeutic” as well as “therapeutic” period tumor growth rates (both diameter and volume) of the different histological meningioma subtypes were approximately balanced, whereas in the “post-therapeutic” period tumor growth rates were considerably lower in atypical meningiomas than in anaplastic meningiomas.

A further analysis using RECIST-criteria during treatment with systemic therapy ("therapeutic" period) revealed stable disease (defined as ≤ 30% decrease or ≥ 20% increase in the maximum tumor diameter) in 25 patients and progressive disease (defined as ≥ 20% increase in the maximum tumor diameter) in 12 cases as the best responses during the treatment periods (see Supplement 4).

Analysis of peritumoral edema

Changes of peritumoral edema were defined as the change rates of maximum peritumoral edema volume over a period of time and were evaluated during the "pre-therapeutic" period in 12 meningiomas, during the "therapeutic" period in 36 meningiomas and during the "post-therapeutic" period in 25 meningiomas. In the overall cohort, mean change rates of peritumoral edema volume were positive in all time periods and were highest in the "pre-therapeutic" and lowest in the "post-therapeutic" period (**Table 3, Figure 1C**). Comparing edema volume change rates between the patient populations treated with different therapies, a decrease in edema volume was evident exclusively in the "therapeutic" period in patients treated with bevacizumab with a change rate of -0,007 cm^3/t (SD=0.0210) (resulting in a reduction of peritumoral edema change rate of 107% compared to the "pre-therapeutic" period), whereas all other included therapies together showed an average increase in peritumoral edema change rate of 0,1070 cm^3/t (SD=0.2350) (resulting in an increase of peritumoral edema change rate of 7% compared to the "pre-therapeutic" period). The remarkable effect of bevacizumab on peritumoral edema change rates during the therapy period in comparison to all other included systemic therapies is visualized in **Figure 2C**.

A reduction in peritumoral edema volume change rate by 29% compared to the "pre-therapeutic" period was detected during the application of chemotherapy, while in case of

somatostatin analogues and tyrosine kinase inhibitors peritumoral edema showed an increase in the peritumoral edema change rates with 95% and 15% respectively. After the termination of systemic therapy no change of peritumoral edema volume was determined in the "chemotherapy" subgroup. The second lowest peritumoral edema change rate after termination of systemic therapy was determined in the "bevacizumab" cohort, whereas patients who were treated with somatostatin analogues or tyrosine kinase inhibitor showed the highest post-therapeutic peritumoral edema change rates.

Moreover, peritumoral edema change rates were evaluated with regard to the different histological meningioma subgroups in **Table 2**. Remarkably, peritumoral edema volume change rates were lower in atypical meningiomas in the "pre-therapeutic" as well as in the "therapeutic" period than in anaplastic meningiomas, while there was almost no difference in the "post-therapeutic" period. Moreover, during systemic therapy atypical meningiomas showed increased peritumoral edema change rates while the peritumoral edema in anaplastic meningiomas decreased in comparison to the "pre-therapeutic" period. After systemic therapy peritumoral edema volumes showed the lowest change rates in atypical as well as anaplastic meningiomas in comparison to the "pre-therapeutic" and "therapeutic" period.

DISCUSSION

The role of systemic therapies in recurrent WHO II and III meningiomas is ill defined. So far, medical therapy of these tumors has only been evaluated in case reports, retrospective patient series and small and uncontrolled prospective studies. The 6 month progression free survival (PFS-6) rates reported among these studies show a high variability and range from 3% to 64.3%. A recent systematic analysis proposed a PFS-6 rate of 26% as benchmark for historical comparisons.[14] Considering this benchmark, hydroxyurea, octreotide analogues, gefitinib and erlotinib were deemed ineffective [4,13,16] while antiangiogenic drugs including bevacizumab, vatalanib and sunitinib showed potential activity with PFS-6 rates of 37.5% to 64.3%.[11,14,17,18,19] Interestingly, our data support a potential role of anti-angiogenic treatment in recurrent WHO II and III meningioma, as the most pronounced decrease of tumor growth rates was observed in patients put on bevacizumab therapy. Of note, however, we observed evidence for drug -induced tumor growth inhibition also for the other types of systemic therapies analyzed in our series, although to considerably smaller extent than for bevacizumab. The activity of bevacizumab or other anti-angiogenic agents targeting the vascular endothelial growth factor (VEGF) pathway in WHO II and III meningioma seems rational from a pathobiological point of view, as prominent expression of VEGF and its receptors as well as neo-angiogenesis have repeatedly been shown in this tumor type.[20,21] Ongoing prospective studies (NCT00972335, NCT01125046) will provide more data on the role of bevacizumab for aggressive meningiomas. A point of caution, however, may be deduced from our observation of increased growth rates after cessation of bevacizumab therapy that were not noted in patients treated with other drugs. “Rebound effects” characterized by more malignant behavior after termination of bevacizumab therapy have

been described for vestibular schwannoma and further studies should address this issue also in meningioma.[22]

Bevacizumab has shown considerable and clinically relevant anti-edematous properties in gliomas and brain metastases. Our data indicate that this effect is also relevant in meningioma patients, as we saw shrinking of peritumoral edema volumes exclusively in patients under bevacizumab treatment. This finding is well in line with reports showing an important role for VEGF in edema formation in meningioma.[23-25] Thus, bevacizumab treatment may be of particular clinical benefit in meningioma patients with symptomatic peritumoral edema and may help to decrease symptomatic burden and corticosteroid need.

Our study has several limitations; despite the multicenter approach, we were able to assemble only a relatively small patient cohort in this rare tumor type. In a number of cases we were unfortunately not able to retrospectively retrieve the neuroimages (or only neuroimages of insufficient quality), because they were done at external institutions. To overcome the individual bias of heterogenic time periods between the MR follow up examinations at each center, growth rates, which were defined as maximum change in tumor diameter or tumor volume over a period of time, were used. Another limitation is the heterogeneity of administered treatments and the retrospective mode of data analysis. Overall, it is important to note that our analyses are strictly descriptive and need to be carefully interpreted and validated by larger, optimally prospective investigations. In general, the lack of reductions in tumor sizes seen with systemic agents suggests that response rate is not an optimal endpoint for clinical trials with medical therapies in meningiomas, but that progression-free survival times or the change in growth rates may be more appropriate end-points. In any case, our study emphasizes the need for standardisation of imaging protocols and clinical management

algorithms in aggressive meningioma patients to overcome the wide variation in clinical practice.

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Figure 1: Visualization of change gradients of tumor diameter (A), tumor volume (B) and peritumoral edema (C) before (continuous-lines), during (dashed-lines) and after (dotted-lines) systemic therapy. The slopes describe the direction (decrease or increase) and steepness (intensity) for the three groups respectively. A very steep line therefore indicates a rapid increase. As clearly visible growth velocity for all three measures (diameter growth rate, volume growth rate, edema change rate) degrades from before to after therapy.

Figure 2: Growth rates expressed as lesion diameter (A) or volume (B) shown for different systemic therapies (black lines = bevacizumab, blue lines = chemotherapy, green lines = somatostatin analogues, magenta lines = tyrosine kinase inhibitor) in the “therapeutic” and “post-therapeutic” period. Since the growth rate of lesion diameter after administration of tyrosine kinase inhibitor was zero, no magenta line is shown in this section. Column C represents the changes of peritumoral edema volumes shown for bevacizumab (black line) versus all chemotherapies, somatostatin analogues and tyrosine kinase inhibitors pooled (red line) during therapy application. The slopes describe the direction (decrease or increase) and steepness (intensity) for the three groups respectively. A very steep line therefore indicates a rapid increase.